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## Scandium trifluoromethanesulfonate as a recyclable catalyst for efficient methoxymethylation of alcohols

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Abstract—Scandium triflate  $[Sc(OTf)_3]$  has been found to be a recyclable catalyst for mild highly efficient methoxymethylation of a variety of alcohols using formaldehyde dimethyl acetal (FDMA).

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Although tetrahydropyranylation is a commonly used method for the protection of hydroxy functions,<sup>1</sup> methoxymethylation has the advantage over tetrahydropyranylation in many instances because the latter involves the formation of a new asymmetric center, thus forming diastereomers when it is used for chiral alcohols.<sup>2</sup> Methoxymethyl (MOM) derivatives are frequently prepared by alkylation of alcohols with an excess of chloromethyl methyl ether in alkaline solution.<sup>1,3</sup> Because of the potent carcinogenic properties of chloromethyl methyl ether,<sup>4</sup> efforts were undertaken to find an alternative safe method for the preparation of MOM ethers. A few reports based on formaldehyde dimethyl acetal (FDMA), an inexpensive reagent, have appeared in the literature utilizing various catalysts such as  $P_2O_5$ ,<sup>5</sup> *p*-toluenesulfonic acid,<sup>6</sup> Nafion-H,<sup>7</sup> TMSI,<sup>8</sup> molybdenum(VI) acetyl acetonate,<sup>9</sup> BF<sub>3</sub>,<sup>10</sup> Envirocat,<sup>11</sup> sulfated zirconia,<sup>12</sup> expansive graphite,<sup>13</sup> and FeCl<sub>3</sub> dispersed on molecular sieves 3 Å.<sup>14</sup> Very recently, it has also been shown that methoxymethyl-2pyridyl sulfide (MOM-ON) is an efficient and neutral methoxymethylating reagent when used in conjunction with AgOTf, NaOAc and THF.<sup>15</sup> However, although these methods have shown an improvement in many instances, many of them suffer from drawbacks such as using stoichiometric amounts of expensive reagents,<sup>15</sup> strong protic acid conditions or destruction of the catalyst during the work-up procedure. Recently, scandium triflate has been introduced as a promising mild and selective reagent for a variety of functional group transformations.<sup>16</sup> While most Lewis acids are decomposed or deactivated in the presence of water or protic solvents,  $Sc(OTf)_3$  is stable and works as a Lewis acid even in aqueous solutions.<sup>17</sup> Thus, unlike other traditional Lewis acids, Sc(OTf)<sub>3</sub> does not decompose under aqueous work-up conditions and its recycling is often possible. This makes Sc(OTf)<sub>3</sub> relatively environmentally acceptable as a catalyst in functional group transformations. This catalyst has been successfully used for a wide range of synthetic organic reactions,<sup>16</sup> especially as a Lewis acid in aldol condensation reactions,<sup>18</sup> Diels-Alder reactions,<sup>19</sup> Friedel-Crafts acylation,<sup>20</sup> Michael reactions,<sup>21</sup> and Fries rearrangements.<sup>22</sup> There is no report of the application of  $Sc(OTf)_3$  as a catalyst for direct methoxymethylation of alcohols. In this paper, we wish to disclose an efficient method for preparing MOM ethers from alcohols by employing formaldehyde dimethyl acetal (FDMA) using a catalytic amount of Sc(OTf)<sub>3</sub>.<sup>23</sup> Table 1 summarizes the results and shows the efficiency of the present protocol for both activated and deactivated benzyl alcohols including sterically hindered ones such as 2,6dichlorobenzyl alcohol (entries 1–6).

Primary, as well as secondary alcohols effectively reacted with an excess of FMDA and 5 mol% of  $Sc(OTf)_3$  in refluxing CHCl<sub>3</sub> to afford the corresponding MOM ethers in good to excellent yields (Table 1, entries 7–13). It is worth mentioning that by employing this protocol even hindered tertiary alcohols such as 1-adamantanol and 1-methyl cyclohexanol also furnished the corresponding MOM-ethers in satisfactory yields (Table 1, entries 14, 15). Neither double bond migration nor elimination was observed in the case of either allylic or tertiary alcohols (Table 1, entries 12–

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Table 1. Methoxymethylation of alcohols using FDMA in the presence of  $Sc(OTf)_3$ 

Entry	Alcohol	Time (h)	Yield(%) <sup>a, b</sup>
1	4-BrC.H.CH.OH	3	08
1	4-DIC <sub>6</sub> 11 <sub>4</sub> C11 <sub>2</sub> O11	5	30
2	$4-CIC_6H_4CH_2OH$	3	90
3	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> OH	4	94
4	$4\text{-}NO_2C_6H_4CH_2OH$	5	94°
5	2,6-(Cl) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> CH <sub>2</sub> OH	4	95
6	c-C <sub>6</sub> H <sub>11</sub> CH <sub>2</sub> CH <sub>2</sub> OH	3	98
7	PhCH <sub>2</sub> CH <sub>2</sub> OH	4	90
8	Ph(CH <sub>2</sub> ) <sub>2</sub> CH <sub>2</sub> OH	4	92

9 
$$6$$
 92  
10 HO OH 7  $82^d$ 

~ . .

	HO		
14	С	8	91
15	Пон	7	77

(a) Isolated Yield. (b) The ratios of subst./FDMA/Sc(OTf)<sub>3</sub> were 1:50:0.05 and all reactions were performed in refluxing CHCl<sub>3</sub>.
(c) The reaction was performed using recovered Sc(OTf)<sub>3</sub>. (d) Yield refers to isolated pure bis-MOM ether.

14). However, our preliminary examination showed that the method is not applicable for protection of hydroxy groups in phenols, because mixtures of unidentified products were formed even at room temperature.

In this protocol, we have also found that  $Sc(OTf)_3$  can be effectively recovered from the reaction mixture during the work-up procedure by simple evaporation of the aqueous phase and drying the solid residue at 90°C overnight. The percentage recovery in most cases was more than 91%. Moreover, efficient methoxymethylation of 4-nitrobenzyl alcohol using recovered  $Sc(OTf)_3$ clearly shows that the reactivity of the recovered catalyst does not change considerably after the work-up (Table 1, entry 4). This undoubtedly renders the above protocol environmentally acceptable.

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## References

- (a) Greene, T. W.; Wuts, P. G. M. Protective Groups in Organic Synthesis, 2nd ed.; Wiley: New York, 1991; (b) Kocienski, P. J. Protecting Groups; Thieme: Stuttgart, 1994.
- Reese, C. B.; Saffhill, R.; Sulton, J. E. J. Am. Chem. Soc. 1967, 89, 3366–3368.
- 3. Herz, J. E.; Lucero, J.; Santoyo, Y.; Waight, E. S. Can. J. Chem. 1971, 49, 2418–2419.
- Occupational Safety and Health Administration, U.S. Department of Labor, Federal Register 39 (20); US Government Printing Office: Washington, DC, 1974.
- 5. Fuji, K.; Nakano, S.; Fujita, E. Synthesis 1975, 276-277.
- 6. Yarley, J. P.; Fletcher, H. Synthesis 1976, 244.
- Olah, G. A.; Husain, A.; Gupta, B. G. B.; Narang, S. C. Synthesis 1981, 471–472.
- Olah, G. A.; Husain, A.; Narang, S. C. Synthesis 1983, 896–897.
- 9. Kantam, M. L.; Santhi, P. L. Synlett 1993, 429-430.
- Danheiser, R. L.; Romines, K. R.; Koyama, H.; Gee, S. K.; Johnson, C. R.; Medich, J. R. Org. Synth. 1992, 71, 133–139.
- 11. Bandgar, B. P.; Hajare, C. T.; Wadgaonkar, P. P. J. Chem. Res. (S) 1996, 90–91.
- Jin, T. S.; Guo, J. J.; Yin, Y. H.; Zhang, S. L.; Li, T. S. J. Chem. Res. (S) 2002, 188–189.
- 13. Jin, T. S.; Li, T. S.; Gao, Y. T. Synth. Commun. 1998, 28, 837–841.
- 14. Patney, H. K. Synlett 1992, 567-568.
- Marcune, B. F.; Karady, S.; Dolling, U. H.; Novak, T. J. J. Org. Chem. 1999, 64, 2446–2449.
- For a review, see: Kobayashi, S. *Eur. J. Org. Chem.* **1999**, *1*, 15–27 and also see: Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. W.-L. *Chem. Rev.* **2002**, *102*, 2227– 2302.
- 17. Kobayashi, S. Synlett 1994, 689-701.
- Crotti, P.; Bussol, V. D.; Favero, L.; Psero, M. J. Org. Chem. 1996, 61, 9548–9552.
- Kobayashi, S.; Hachiya, I.; Araki, M.; Ishitani, H. Tetrahedron Lett. 1993, 34, 3755–3758.
- 20. Kawada, A.; Mitamura, S.; Kobayashi, S. *Synlett* **1994**, 545–546.
- 21. Kobayashi, S.; Hachiya, I.; Ishitani, H.; Araki, M. Synlett **1993**, 472–474.

- 22. Kobayashi, S.; Moriwaki, M.; Hachiya, I. J. Chem. Soc., Chem. Commun. 1995, 1527–1528.
- 23. General procedure for the preparation of MOM ethers: To a solution of alcohol (2 mmol) and FDMA (100 mmol) in CHCl<sub>3</sub>, Sc(OTf)<sub>3</sub> (0.1 mmol) was added and the mixture was stirred at reflux until complete disappearance of starting alcohol (as monitored by TLC). After completion, the reaction was quenched with distilled water (20 mL), and the mixture was extracted with CHCl<sub>3</sub> (2×30

ml). The aqueous layer was separated and evaporated under reduced pressure to afford the recycled catalyst. The organic layer was washed successively with a 10% aqueous solution of NaOH (25 mL) and water (15 ml) and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Evaporation of the solvent under reduced pressure gave the almost pure MOM ether. Further purification of products could be achieved by vacuum distillation or recrystallization to afford the corresponding pure MOM ethers (Table 1).